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Expression of H3.3 G34W Distinguishes Giant Cell Tumor of Bone From Its Major Giant Cell-containing Bone and Soft Tissue Mimics, in Particular Aneurysmal Bone Cyst and Giant Cell Tumor of Soft Tissue

To the Editor:

Giant cell tumor of bone (GCTB) is a locally aggressive bone neoplasm, predominantly of long bones, with a predilection for young adults. Histologically, they are composed of histiocytoid to spindled mononuclear cells, admixed with large osteoclastic giant cells. GCTB has to be differentiated from other giant cell-containing lesions of bone that may have histologic similarities with GCTB, including chondroblastoma, nonossifying fibroma, brown tumor of hyperparathyroidism, tenosynovial giant cell tumor invading bone and primary aneurysmal bone cyst (ABC). In the classical clinical and radiologic setting, GCTB does not pose a major diagnostic challenge. However, in my personal experience, due to the morphologic intratumoral heterogeneity in GCTB, including prominent secondary ABC changes, the distinction between GCTB with predominantly secondary ABC changes and primary ABC can be extremely challenging (and sometimes impossible to make). This is especially the case in small biopsies of lesions with an atypical radiologic and/or clinical presentation. The presence of a histone *H3F3A* (*H3.3*) gene mutation involving a substitution in glycin 34 was reported in 96% of GCTB, the vast majority of which are represented by G34W resulting from a GGG > TGG nucleotide change.[1–3] Moreover, these point mutations of the *H3F3A* gene were not observed in the other giant cell-containing mimics of bone (including ABC) and soft tissue, including giant cell tumor of soft tissue, which is a rare tumor with striking histologic resemblance to GCTB.[4] Interestingly, a monoclonal antibody has been developed targeting the mutational site G34W of the histone variant H3.3.[3,5] Recently, Lüke et al[5] reported that a positive staining for the monoclonal antibody (clone RM263) detecting the H3.3 G34W mutation is a strong indicator of the *H3F3A* mutation in GCTB and therefore can be used as a valuable sensitive and specific diagnostic tool in differentiating GCTBs from other giant cell-containing lesions of the bone and soft tissue. However, Lüke and colleagues did not explore extensively GCTB cases with morphologic striking secondary ABC changes

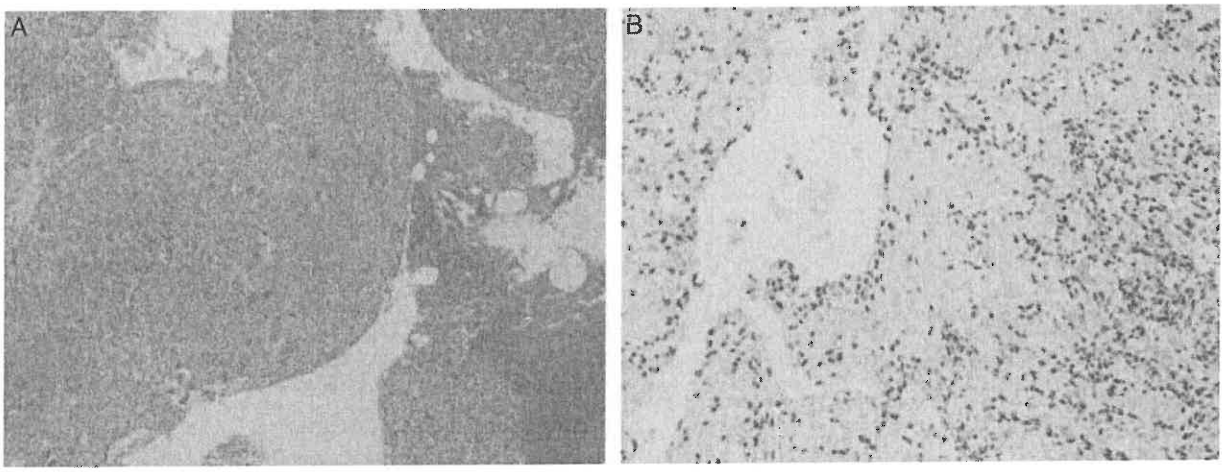

FIGURE 1. A, Histomorphology of a giant cell tumor of bone with extensive secondary aneurysmal bone cyst change, in areas indistinguishable from a primary aneurysmal bone cyst (H&E, original magnification, ×40). B, H3.3 G34W is diffusely expressed by the stromal cells. The osteoclastic giant cells are negative for H3.3 G34W expression (original magnification, ×100). H&E indicates hematoxylin and eosin.

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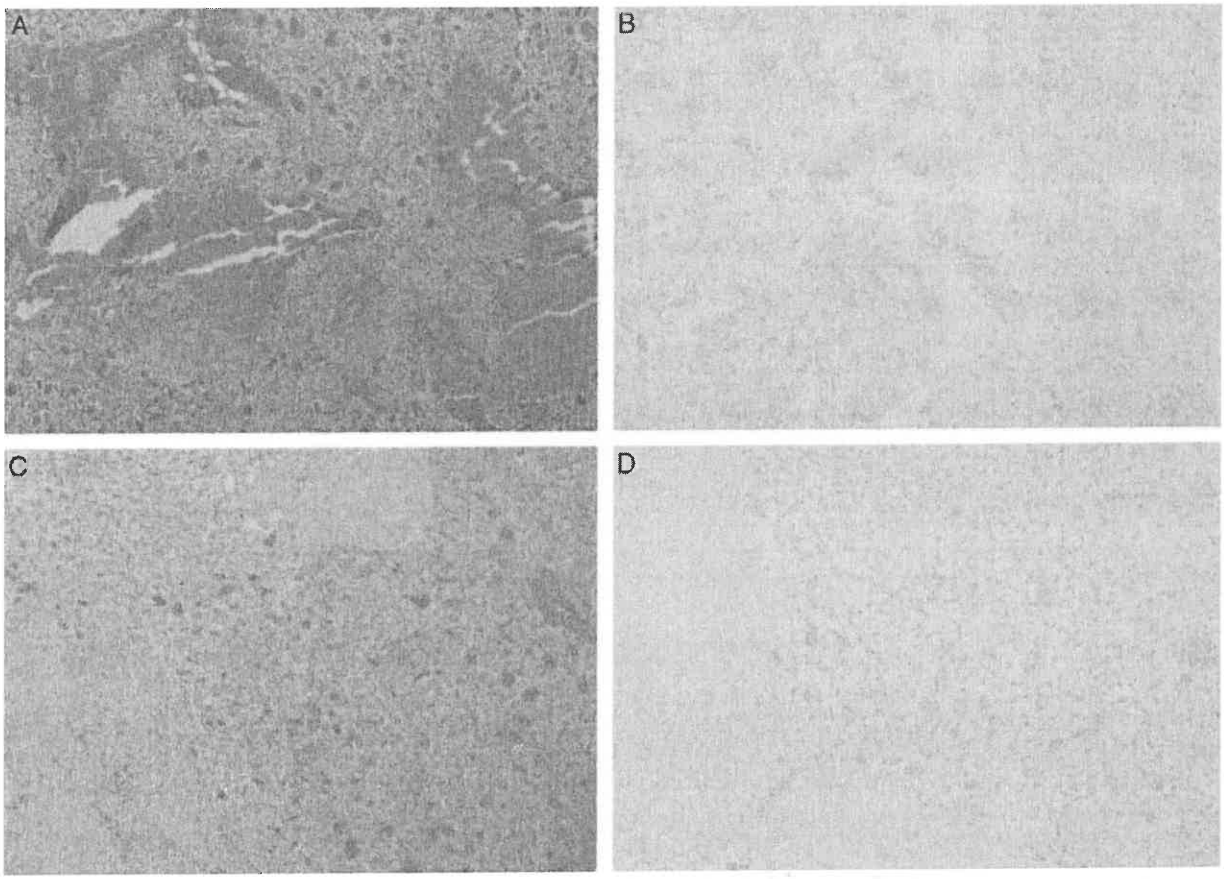

FIGURE 2. A, Histomorphology of a primary aneurysmal bone cyst (H&E, original magnification, ×40). B, All tumor cells are negative for H3.3 G34W staining (original magnification, ×100). C, Histomorphology of a giant cell tumor of soft tissue (H&E, original magnification, ×40). D, No expression for H3.3 G34W in the tumor cells (original magnification, ×100). H&E indicates hematoxylin and eosin. full color online

and giant cell tumors of soft tissue, which could be major histologic mimics of GCTB.

Therefore, we used in our study the same H3.3 G34W rabbit monoclonal antibody (clone RM263, RevMab Biosciences) (1:400) for analysis of 14 GCTBs (all with extensive secondary ABC changes), 12 clinically/radiologically classical ABCs, and 4 giant cell tumors of soft tissue. In 4 of 12 ABC cases, the diagnosis was confirmed by demonstrating rearrangement of *USP6* region using fluorescence in situ hybridization analyses. All the GCTB samples showed a strong and consistent nuclear staining in the stromal cells with negative staining of the osteoclastic giant cells. By contrast, all cells in the ABCs and giant cell tumors of soft tissue were completely negative (Figs. 1, 2).

In conclusion, we have showed with this study that GCTBs with secondary ABC changes can be diagnosed by the monoclonal antibody detecting the H3.3 G34W mutation, differentiating them from primary ABCs and giant cell tumors of soft tissue. This antibody could therefore be used as a valuable diagnostic tool when facing giant cell-containing bone and soft tissue lesions, particularly in challenging specimens with scarce material and/or atypical imaging or clinical presentation.

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REFERENCES

1. Behjati S, Tarpey PS, Presneau N, et al. Distinct *H3F3A* and *H3F3B* driver variants define chondroblastoma and giant cell tumour of bone. *Nat Genet*. 2013;45:1479–1482.
2. Presneau N, Baumhoer D, Behjati S, et al. Diagnostic value of H3F3A mutations in giant cell tumour of bone compared to osteoclast-rich mimics. *J Pathol Clin Res*. 2015;1:113–123.
3. Amary F, Berisha F, Ye H, et al. H3F3A (Histone 3.3) G34W immunohistochemistry: a reliable marker defining benign and malignant giant cell tumor of bone. *Am J Surg Pathol*. 2017;41:1059–1068.
4. Lee JC, Liang CW, Fletcher CD. Giant cell tumor of soft tissue is genetically distinct from its bone counterpart. *Mod Pathol*. 2017;30:728–733.
5. Lüke J, von Baer A, Schreiber J, et al. H3F3A mutation in giant cell tumour of bone is detected by immunohistochemistry using a monoclonal antibody against the G34W mutated site of the histone H3.3 variant. *Histopathology*. 2017;71:125–133.